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A Successful Application of the Concept of Making Use of Hydrophobic Forces to Prepare Large-ring Compounds[1]

Xi-Kui Jiang,* Yong-Zheng Hui, and Zeng-Xiang Fei
Shanghai Institute of Organic Chemistry, Academia Sinica, 345 Lingling Lu, Shanghai, 200032, China

The yields of the 16-membered-ring intramolecular cycloaddition products, β-truxinate (**4**) and δ-truxinate (**5**), can be greatly increased by making use of the hydrophobic or entropy-driven forces in aggregating media.

The formation of a macrocyclic ring from a flexible chain demands a formidable price in terms of entropy,[2,3] and chemists have resorted to energetically highly favoured reactions between the end-groups in order to synthesize large-ring compounds.[4—9] However, a new approach could be to use forces which will greatly reduce the entropy expense. Recently we demonstrated that the two ends of a long-chain molecule can be forced to interact by making use of the entropy-driven hydrophobic-lipophilic forces.[10—12] Here we report the first successful attempt at applying this concept to the preparation of a macrocyclic compound, and of demonstrating that hairpin-looping in hydrophilic or aggregating media is an entropy-driven process.

In acetonitrile, Kuzuya and Williams[13,14] have achieved an intramolecular [2 + 2] cycloaddition of the 1,2-dicinnamoxyethane (**1**) and the 1,10-dicinnamoxydecane (**2**) to yield the β-truxinates (**3**) and (**4**) as *cis*-adducts, and the δ-truxinate (**5**) as a *trans*-adduct (Scheme 1). Their yields were good for (**3**) (90%) but very poor for (**4**) and (**5**) (6—7%). We have now made a systematic investigation of the effects of hydrophilicity of the media on the yields[15] and rates[16] of this intramolecular cycloaddition. The nine organic solvents chosen to form H_2O–organic mixtures were (listed in the order of increasing lipophilicity)[17]: $HOCH_2CH_2OH$ (EG), Me_2SO, $MeOCH_2CH_2OH$ (MEC), dimethylformamide (DMF), dioxane (DX), MeCN, acetone, EtOH, Bu^tOH.

Table 1 shows that solvophobic forces have indeed played a major role in the formation of macrocyclic compounds. Comparing the total yields of (**4**) and (**5**) at the same composition Φ, they generally decrease with increasing lipophilicity (Σf)[17] of the organic co-solvent. With the same solvent mixture, *e.g.* Me_2SO–H_2O, the yields increase with increasing hydrophilicity, *i.e.*, decreasing lipophilicity or Φ values, of the media. Yields in MeCN, acetone, EtOH, and Bu^tOH (data for the last three not listed in Table 1) are similar at all Φ values. Thus when the lipophilicity of the media reaches a certain level, *e.g.*, that of MeCN, the yield of large-ring intramolecular cycloaddition is no longer dependent on hydrophobic forces. The most pleasing result is that the yields can be raised to 78% in EG–H_2O and to 90% in Me_2SO–H_2O.

However, in comparing the two solvent systems MeCN–H_2O and Me_2SO–H_2O at Φ = 1.0 and 0.3, it was found that the yields (84—87%)† and rates of formation (k = 0.03 to 0.04 min^{-1})† of the 'small-ring' adduct (**3**) from (**1**) are practically unaffected by the great differences in solvent aggregating power or hydrophobicity. Evidently, the intrinsic reactivity of this photochemical reaction is essentially independent of the nature of the medium. This means that conventional kinetic methods could be applicable to the study of the reaction (**2**) → (**4**) + (**5**) and the measured rate constants of the formation of (**4**) + (**5**) in Table 2, *i.e.*, $k_{(4)\,+\,(5)}$, could be a direct reflection of the thermal conformational (coiling) processes which are highly dependent on hydrophobic forces. Possibly, pre-association of the reacting groups[12,18] could very well be involved and be rate-determining.

In fact, our results (Table 2) are fully consistent with the above-mentioned hypothesis and in a more than just qualitat-

Table 1. Total yields (%) of (**4**) and (**5**) in six aquaorgano solvents of various compositions (Φ = graded volume fraction of the organic component).[a]

Φ	EG	Me_2SO	MEC	DMF	DX	MeCN
1.0	21	16	12	9	11	5
0.6	50	31	30	27	18	14
0.5	72	68	42	29	21	12
0.4	71	73	45	29	24	11
0.3	78	90	48	39	26	18

[a] The yields were quantitatively measured by h.p.l.c., with an experimental uncertainty of 5%. The pure products (**4**) and (**5**) have been isolated. The concentration of (**2**) was 8.3×10^{-6} M.

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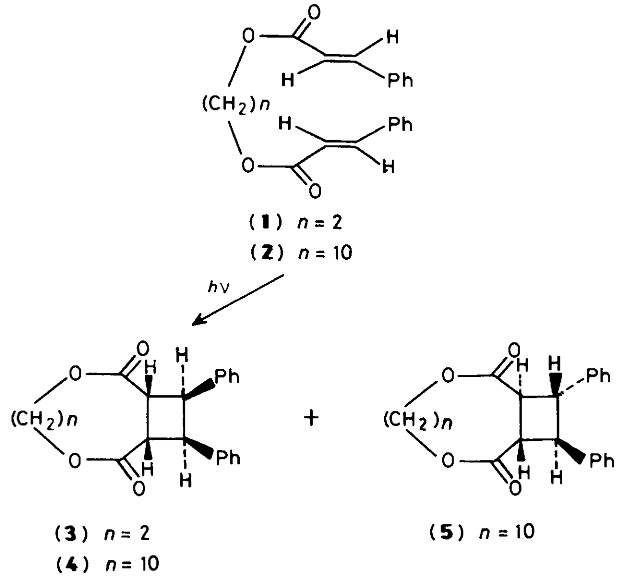
† At 34 °C, [(**1**)] = 4.3×10^{-4} M, error is ±5%. At 19 °C, [(**1**)] = 2.8×10^{-4} M, error is ±10%.

Table 2. The rate constants k^a and activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for the formation of (4) + (5) at composition Φ in $Me_2SO–H_2O$ and $DX–H_2O$.

	Me_2SO-H_2O			$DX-H_2O$		
Φ	k/min^{-1}	$\Delta H^\ddagger/$ kcal mol^{-1}	$\Delta S^\ddagger/$ cal mol^{-1} K^{-1}	k/min^{-1}	$\Delta H^\ddagger/$ kcal mol^{-1}	$\Delta S^\ddagger/$ cal mol^{-1} K^{-1}
0.60	0.032	8.8 ± 0.5	−5.53 ± 0.38	0.0029	8.7 ± 0.3	−10.6 ± 0.6
0.50	0.061	8.5 ± 0.6	−3.99 ± 0.29	0.0034	9.0 ± 0.6	−9.74 ± 0.71
0.45	0.12	—	—	0.0050	—	—
0.40	0.31	9.2 ± 0.6	−0.77 ± 0.11	0.0069	8.9 ± 0.5	−9.45 ± 0.62
0.35	0.37	—	—	0.0093	—	—
0.30	0.67	9.1 ± 0.5	1.10 ± 0.12	0.011	8.9 ± 0.6	−8.23 ± 0.45

[a] The rate constants were determined by h.p.l.c. at 34 °C. The experimental uncertainties are *ca.* 8.5% for k. 1 cal = 4.184 J.



Scheme 1

ive way. For example, in the $Me_2SO–H_2O$ system in the Φ range of 0.30—0.60, k is actually linearly related to the solvent aggregating power, *i.e.*, $\log k = -4.8\ \Phi + 1.2$ (r = 0.985). More notably, while the $\Delta H^\ddagger$ values are not much affected by changes in Φ, there is a linear dependence of $\Delta S^\ddagger$ on Φ, *i.e.*, $\Delta S^\ddagger = -23.1\Phi + 8.1$ (r = 0.991; $\Delta G^\ddagger = 5.5\Phi + 7.1$, r = 0.986).‡ As Table 2 shows, from Φ = 0.6 to 0.3, $\Delta S^\ddagger$ increases from −5.5 to + 1.1 cal mol^{-1} K^{-1}. In other words, we have apparently monitored an entropy-favoured process. The present results, therefore, could be a rare piece of evidence for the idea that self-coiling in aggregating media, just like aggregation, is an entropy-favoured process.[10a,19]

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References

1 For part 12 of 'The Effect of Hydrophobic-Lipophilic Interactions on Chemical Reactivity,' see X.-K. Jiang, X.-Y. Li, and B.-Z. Huang, *J. Phys. Org. Chem.*, 1988, **1**, in the press.

2 (a) H. E. Oneal and S. W. Benso, *J. Chem. Eng. Data,* 1970, **15**, 266; (b) M. I. Page and W. P. Jencks, *Proc. Natl. Acad. Sci. USA,* 1971, **68**, 1678.

3 (a) G. Illuminati and L. Mandolini, *Acc. Chem. Res.*, 1981, **14**, 95; (b) L. Mandolini, in 'Advanced Physical Organic Chemistry,' vol. 22, eds. V. Gold and D. Bethell, Academic Press, London, 1986, p. 1—112, and references cited therein.

4 E. J. Corey, K. C. Nicolaon, and L. S. Melvin, *J. Am. Chem. Soc.*, 1975, **97**, 653, 654, and references cited therein.

5 H. Gerlach and A. Thalmann, *Helv. Chim. Acta,* 1974, **57**, 266.

6 K. Narasaka and T. Mukaiyama, *Chem. Lett.*, 1978, 885, and references cited therein.

7 N. W. Porter, *J. Am. Chem. Soc.*, 1986, **108**, 2787.

8 S. Masamune, S. Kamata, and W. Schilling, *J. Am. Chem. Soc.*, 1975, **97**, 3515.

9 K. Lloyd and G. T. Yong, *Chem. Commun.*, 1968, 1400.

10 (a) X.-K. Jiang, W.-Q. Fan, and Y.-Z. Hui, *J. Am. Chem. Soc.*, 1984, **106**, 7202; (b) X.-K. Jiang, W.-Q. Fan, Y.-Z. Hui, J.-H. Gu, and M.-F. Cheng, *Acta Chem. Sin.*, 1987, **45**, 900; *Eng. Ed.*, 1987, 98.

11 X.-K. Jiang, Y.-Z. Hui, and W.-Q. Fan, *J. Am. Chem. Soc.*, 1984, **106**, 3839.

12 X.-K. Jiang, Y.-Z. Hui, and Z.-X. Fei, *J. Am. Chem. Soc.*, 1987, **109**, 5862.

13 J. L. R. Williams, S. Y. Farid, J. C. Doty, R. C. Daly, D. P. Speeht, R. Searle, D. G. Bordon, H. J. Chang, and P. A. Martic, *Pure Appl. Chem.*, 1977, **49**, 523.

14 (a) M. Kuzuya, M. Tanaka, and T. Okuda, *Tetrahedron Lett.*, 1983, **24**, 4237; (b) M. Kuzuya, M. Tanaka, M. Hosoda, A. Noguchi, and T. Okuda, *Bull. Chem. Soc. Jpn.*, 1984, 22.

15 We separated the previously reported products (4) and (5) by h.p.l.c. and identified them by n.m.r., m.s. and elemental analysis. The n.m.r. of (4) has two doublets at δ 4.01 and 4.62, and (5), two doublets at δ 3.21 and 3.59, in agreement with the literature, *cf.* (a) P. L. Egerto, E. M. Hyde, J. Trigg, A. Payne, P. Beynon, M. V. Mijovic, and A. Reiser, *J. Am. Chem. Soc.*, 1981, **103**, 3859; (b) G. Montaudo and S. Caceamese, *J. Org. Chem.*, 1973, **38**, 710.

16 Under our experimental conditions, 5% of the *trans, trans* starting material (2) undergoes *cis-trans* isomerization to two other isomers (*cis, trans* and *cis, cis*) *cf.* (a) F. D. Lewis, J. D. Oxman, L. L. Gibson, H. L. Hampsch, S. L. Quillen, *J. Am. Chem. Soc.*, 1986, **108**, 3005; (b) J. Rennert, S. Soloway, I. Waltdrer, and B. Lerg, *J. Am. Chem. Soc.*, 1972, **94**, 7242. We have separated and identified (m.s., n.m.r.) these isomers. Since products (4) and (5) are not entirely stable, our reported yields obtained after 10—50 h or 60—300 half-lives are not accurate indicators of rate; our rate constants were measured at the initial stage (2—4 half-lives) of the reaction.

17 (a) R. F. Rekker, 'Hydrophobic Fragmental Constants,' vol. 1, Elsevier, Amsterdam, 1977; (b) X.-K. Jiang, Y.-Z; Hui, and W.-Q. Fan, *Acta Chim. Sin.*, 1984, **42**, 1276; *Eng. Ed.*, 1985, 111; (c) W.-Q. Fan and X.-K. Jiang, *J. Am. Chem. Soc.*, 1985, **107**, 7680; (d) X.-K. Jiang, X.-Y. Li, and B.-Z. Huang, *Proc. Indian Acad. Sci.* (*Chem. Sci.*), 1987, **98**, 409.

18 F. M. Winnik, M. A. Winnik, S. Tazuke, and C. K. Ober, *Macromolecules,* 1987, **20**, 38.

19 C. Reichardt, 'Solvent Effects in Organic Chemistry,' Weinheim, New York, 1978, p. 19.

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‡ The dioxane–H_2O system behaved similarly.